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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/393,844	HIGH ET AL.
	Examiner	Art Unit
	Daniel M Sullivan	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 21-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 21-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Non-Final Office Action is a response to the "Amendment in Response to Office Action" of 28 August 2003 (hereinafter, 28 August Paper) filed in response to the Non-Final Office Action mailed 24 February 2003 (hereinafter, 24 February Office Action). Claims 1-9 and 21-28 were considered in the 24 February Office Action. Claims 9 and 22-28 were amended in the 28 August Paper. Claims 1-9 and 21-28 are pending and under consideration.

Response to Amendment

Claim Rejections - 35 USC § 103

Claim 9 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Weiner in view of Crabtree *et al.* for reasons of record. As pointed out in the 24 February Office Action, Applicant's arguments regarding the patentability of the claim are based on the limitation of claim 1 to a virus. However, claim 9 is directed to a kit including the vector of claim 1, which is comprised within the virus of claim 1. Therefore, claim 9 is not limited to a virus and remains unpatentable over the prior art for the reasons of record. It appears that Applicant has attempted to amend the claim in the 28 August Paper, however the markings are such that "virus" is lined through and "vector" is in brackets. As these markings are commonly understood to indicate insertion of the word in brackets and deletion of the word that is lined through, the claim is understood to still encompass a kit comprising the "vector" of claim 1.

Double Patenting

Applicant is advised that claims 25-28 still read as a substantial duplicate of claims 6-9. Again, Applicant has attempted to amend the claims but the editor's markings used indicate that claims should read the same as the claims previously examined.

Claim Rejections - 35 USC § 112

Claims 1-9 and 21-28 stand rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description for reasons of record and herein below in the response to arguments.

Claims 9 and 28 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for reasons of record. Again, although it appears that Applicant would like to amend the claims, the editor's markings do not indicate any modification of the claim from the previous claim set.

Response to Arguments

Claim Rejections - 35 USC § 112

Claims 1-9 and 21-28 were rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description because a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of DNA's encoding polypeptides having Factor IX biological activity.

In response to the rejection, Applicant argues that, given the teachings of the specification and the understanding of Factor IX structure and function that existed at the time of filing, the full scope of the Factor IX gene of the claims is adequately described. Applicant points to the disclosure of several species homologues of the Factor IX gene in the specification and prior art and provides several Exhibits that teach structural domains that are required for Factor IX functions. Applicant urges that the Exhibits teach the skilled artisan which sequences of Factor IX can be modified without destroying function and, consequently, those skilled in the art would also have known how to produce variant Factor IX sequences having function, and those skilled in the art would have known the Factor IX variants that would not be desirable for optimal Factor IX function.

These arguments have been fully considered but are not deemed persuasive. Although Applicant's arguments are persuasive insofar as the Factor IX gene of the claim has the same activity as wild-type Factor IX, the claims also encompass Factor IX genes that have been mutated such that they possess properties that are superior to native Factor IX. As pointed out in the previous Office Action, the Factor IX of the claims encompasses "mutants of wild-type Factor IX which mutations render it therapeutically effective or more therapeutically effective ([specification], paragraph bridging pages 15 and 16), variants which retain Factor IX biological activity, variants that confer enhanced stability on the protein variants having enhanced specificity of action ([specification] page 16, paragraph 3)" (page 5). Applicant's arguments assert that the skilled artisan would know which amino acids could be mutated such that Factor IX activity is maintained. Even given the teachings cited by Applicant in the response, the skilled artisan could not possibly envision the full scope of Factor IX genes that are "more

therapeutically effective" than the native Factor IX protein because such modification requires more than an understanding of which residues are necessary for function and which residues are dispensable. What is required is knowledge of precisely how the protein can be modified to confer the superior properties. Neither the specification nor the prior art sets forth a description of the Factor IX gene such that the skilled artisan could readily envision all variants that are "more therapeutically effective" than the native Factor IX. Therefore, the claims stand rejected as lacking adequate descriptive support for the Factor IX gene of the claims.

New Grounds

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 and 21-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the composition comprising a Factor IX gene wherein the Factor IX encoded by the gene has the functional properties of the wild type protein or is incapable of binding to collagen, does not reasonably provide enablement for the composition wherein the Factor IX gene is modified such that the protein encoded thereby is "more therapeutically effective" than the wild-type gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims are directed to a virus comprising a recombinant adeno-associated virus vector comprising a Factor IX gene, wherein the Factor IX gene encompasses recombinantly derived mutants of wild-type Factor IX which mutations render it more therapeutically effective, or that confer enhanced stability or enhanced specificity of action (page 16, paragraph 3). The claims therefore broadly encompass a composition comprising a DNA encoding any polypeptide having improved biological activity relative to the biological activity of wild-type human Factor IX. Biological activity is defined in the paragraph bridging pages 18 and 19 of the specification as, "capable of mediating coagulation of blood in a blood coagulation assay."

State of the prior art and level of predictability in the art: The art generally acknowledges that the effect of modifying amino acid sequence on the function of a polypeptide is highly unpredictable. For example, Richards (1997) *Cell Mol. Life Sci.* 53:790-802 teaches, "[i]n terms of structural alterations and thermostability, responses to genetic mutations are context dependent and remain difficult to predict with any confidence" (abstract, column 1). Thus,

Richards teaches that the effect of mutation on protein stability, a prerequisite for biological function, is unpredictable. Richards also teaches that even limited amino acid modifications can have dramatic effects on protein structure and function. In the second column on page 791, Richards cites the example of influenza virus hemagglutinin protein, wherein alterations in the ionization state of just a few ionizable groups dramatically alters the biological behavior of the molecule. Citing a published study of done on the gene V protein, Richards teaches that, in spite of only limited modification at two amino acid positions, "[t]he effects on the overall stability of the protein were remarkably variable" (page 794, column 1). In the paragraph bridging pages 796 and 797, Richards teaches, "[i]n single site mutants, the structural changes are generally greatest near the site of mutation, and moving away, decrease radially in all directions. *Even the small changes are so complex that the linkage relations do not allow assignments of the energetic changes to unique parts of the altered residue and its immediate contacts*" (emphasis added) and "[t]here is no convincing explanation yet of how the changes in binding can produce a major movement over such a distance." Finally, in the first full paragraph in the second column on page 793, Richards teaches, "[a]lmost all mutations are accompanied by some conformational change, making prediction of the effects on stability difficult. *In most cases mutations lead to lowering of the stability*." (emphasis added). Thus, Richards teaches that small changes in the primary structure of a protein frequently have dramatic effects on the higher order structure and function of the protein, and that these effects are highly unpredictable. Given these teachings, the skilled artisan would understand that modifying a Factor IX gene such that it has improved biological activity could not be achieved without making and testing each modification, literally millions of variants.

Amount of direction provided by the inventor and existence of working examples: Although the specification teaches how Factor IX mutants might be generated and tested for biological activity (see especially the paragraph bridging pages 17 and 18) and sets forth an example of a polypeptide considered to have enhanced biological properties (i.e., the lysine to alanine mutant having reduced binding to collagen IV), the disclosure does not instruct the skilled artisan how to make any Factor IX mutant having improved biological activity relative to the biological activity of wild-type human Factor IX. The teachings set forth in the disclosure provide instruction as to how a mutant Factor IX having improved biological activity can be identified, but do not teach the skilled artisan how to construct such mutants without blindly replacing each amino acid in the Factor IX sequence with at least the 19 other naturally occurring amino acids in all possible combinations and testing each mutant for any enhancement of biological activity.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to make the full scope of the claimed invention without having to engage in undue experimentation. In *In re Wands*, the court states, "[t]he determination of what constitutes undue experimentation in a given case requires the application of standard reasonableness, having due regard for the nature of the invention and the state of the art" (at 1404). In the instant case, the claims broadly encompass a vector comprising any Factor IX gene including mutants having enhanced biological activity. However, the art teaches that the effect of mutating proteins on the overall function of the protein is highly unpredictable, and the majority of mutations would be expected to produce proteins having the same or reduced biological activity relative to the wild-

type protein. Therefore, in order to make those embodiments of the invention encompassed by mutants having enhanced biological activity, the skilled artisan must resort to empirical experimentation to make and test all possible mutants of Factor IX. Clearly, given the nature of the invention and the state of the art, the amount of experimentation required is undue according to standard reasonableness.

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3 and 6-8 are rejected under 35 U.S.C. §102(e) as being anticipated by Wilson *et al.* (U.S. Patent 5,866,552).

Claims 1-3 and 6-8 were rejected under 35 U.S.C. §102(e) as anticipated by Wilson *et al.* in the First Office Action on the Merits mailed on 5 December 2000. The rejection was withdrawn in the Office Action mailed 20 May 2002 in view of the Declaration under 37 C.F.R. §1.131 filed 8 June 2001. However, upon reviewing the record, the Examiner has discovered that the Declaration was improper because it was not signed by all of the inventors named on the application (see M.P.E.P. §715.04). Specifically, Although Dr. High identifies herself as a co-inventor of the subject matter claimed and not the sole inventor of the claims at issue, the Declaration is not signed by Roland Herzog the other inventor of the claimed subject matter. As the Declaration is improper, it cannot be relied upon to establish a date of conception prior to the

Wilson *et al.* patent. Therefore, the claims are rejected for the reasons set forth in the 5 December 2000 Office Action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DMS

DAVID GUZO
PRIMARY EXAMINER